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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/748,789	12/22/2000	Anthony P. McHale	11067/1090	3325

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EXAMINER

LI, QIAN J

ART UNIT	PAPER NUMBER
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1632

15

DATE MAILED: 06/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/748,789

Applicant(s)

MCHALE ET AL.

Examiner

Q. Janice Li

Art Unit

1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 17 March 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-4, 10-19, 26, 30-32 and 36-49 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

- 5) ☐ Claim(s) _____ is/are allowed.

- 6) ☒ Claim(s) 1-4, 10, 13-19, 26, 30-32 and 36-49 is/are rejected.

- 7) ☒ Claim(s) 11, 12 is/are objected to.

- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.

- 10) ☒ The drawing(s) filed on 17 March 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some * c) ☐ None of:

1. ☒ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. _____.

3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)

- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.

- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.

- 5) ☐ Notice of Informal Patent Application (PTO-152)

- 6) ☐ Other:

DETAILED ACTION

The amendment filed 3/17/03 has been entered and assigned as Paper No. 14. Claims 5-9, 20-25, 27-29, and 33-35 have been canceled. Claims 1, 2, 4, 10-12, and 30-32 have been amended, claims 36-49 are newly added. Claims 1-4, 10-19, 26, 30-32, and 36-49 are under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated. The arguments in paper #14 would be addressed to the extent that they apply to the current rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 26 stands rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for pre-sensitizing the RBC with eletroporation *in vitro*, does not reasonably provide enablement for pre-sensitizing the RBC with electroporation *in vivo*, for reasons of record in Paper #11.

In the previous Office action, claim 29, rather than claim 26 was rejected under this provision. However, claim 29 had been withdrawn from consideration at the time, thus, clearly, it was a typographic error. Applicants have amended the rest of the rejected claims but claim 26, thus, the rejection to claim 26 stands.

Art Unit: 1632

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 49 is newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 49 recites the limitation "A method according to claim 30". There is insufficient antecedent basis for this limitation in the claim. For the interest of compact prosecution, the claim has been interpreted as further limiting the process recited in claim 30 for examining purpose.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

(f) he did not himself invent the subject matter sought to be patented.

The previous provisional rejection of claims 4, 18, 19 under 35 U.S.C. 102(e) as being anticipated by commonly assigned copending Application No. 09/748,063 which

Art Unit: 1632

has a common inventor with the instant application, is withdrawn in light of the clarification that the applications were commonly owned at the time of Applicant's invention.

The previous rejection of claims 4, 18, 19 under 35 U.S.C. 102(f) is withdrawn in light of the clarification that the applications were commonly owned at the time of Applicant's invention.

Claims 1, 3, 10, 14-17, 26, 30, and 31 stand rejected under 35 U.S.C. 102(f) over U.S. Application No. 09/779,186, now U.S. patent 6,495,351, because the response has not made clear whether the applications are commonly owned *at the time of Applicant's invention*. The rejection applies to claims 36, 37, and 49.

Claims 26, 30, 31, and 49 are newly rejected under 35 U.S.C. 102(b) as being anticipated by *Mouneimne et al* (US 5,236,835).

The claims are drawn to red blood cells loaded with an agent and obtainable by a method as recited in the claims.

Mouneimne et al teach red blood cells loaded with a CD4 or glycoporphin (abstract), wherein the cells are from warm blood animal or human, they are intrinsically immunocompatible if applied to the same individual from which the cells are obtained and they serve as a pharmaceutical composition when they administered to the donor releasing the loaded agent(s). Therefore, *Mouneimne et al* anticipate the instant claims.

Art Unit: 1632

With respect to the method of making the loaded RBCs, the claims encompass presensitizing and loading the cell at the same time, and claim 26 only requires “obtainable”, thus, the red blood cell as claimed is not necessarily obtained from the recited method.

Applicants are reminded in this and following rejections, whether or not the method of loading differs from instantly claimed in the cited references, patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it, which is recited in the claims. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985). Accordingly unless applicants provide factual evidence showing that the red blood cells obtained from the method taught by the reference are structurally different from instantly claimed, they are not patentably distinct. Therefore, *Mouneimne et al* or other references anticipate the instant claims.

Claims 26, 30, 31, and 49 are newly rejected under 35 U.S.C. 102(b) as being anticipated by *Lizano et al* (Biochimica Biophysica Acta 1998;1425:328-336).

Lizano et al teach a red blood cell loaded with two types of enzymes, ADH and ALDH, which is drawn from the Swiss CD1 mice, and immunocompatible in these mice. They administered loaded RBCs to the mice by intravenous injection in a pharmaceutical acceptable carrier; therefore, *Lizano et al* anticipate the instant claims.

Art Unit: 1632

Claims 26, 30, 31, and 49 are newly rejected under 35 U.S.C. 102(b) as being anticipated by *Mitchell et al* (Biotech Applied Biochem 1990;12:264-75).

Mitchell et al teach a human red blood cell loaded with rIL-2 and human serum albumin (page 266). They go on to teach using such as pharmaceuticals (last paragraph, page 274). Therefore, *Mitchell et al* anticipate the instant claims.

Claims 26, 30, 31, and 49 are newly are rejected under 35 U.S.C. 102(b) as being anticipated by *Zimmermann et al* (US 4,289,756).

Zimmermann et al teach a red blood cell loaded with medicaments (example 1). Therefore, *Zimmermann et al* anticipate the instant claims.

Claims 26, 30-32, and 49 are newly are rejected under 35 U.S.C. 102(b) as being anticipated by *Magnani et al* (US 6,139,836).

Claim 32 is drawn to a loaded RBC comprises PEG.

Magnani et al teach using PEG as a pharmaceutically acceptable carrier for in vivo delivery of loaded erythrocytes (column 7, line 63). Therefore, *Magnani et al* anticipate the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

Art Unit: 1632

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 3, 13-17, 26, 30, and 31 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Mitchell et al* (Biotech Applied Biochem 1990;12:264-75), in view of *Ortiz et al* (Mutation Res 1995;327:161-9), and the rejection has been modified to include claims 2, 36, 37, 48, and 49.

Claim 2 is drawn to loading two agents to red blood cells, should have been included in the rejection because both *Mitchell et al* and *Ortiz et al* teach loading two agents to cells. New claims 36 and 37 are substantially identical to claims 16 and 17, and claim 48 is drawn to an additional electrosensitizing step.

In paper #14, applicants argue that *Mitchell et al* does not teach separate steps of sensitization and loading, and *Ortiz et al* teach a method that the electrical treatment and the permeation occur as a single step, not done separately. Applicants further argue that neither *Mitchell* nor *Ortiz* teaches or suggests that electroporated cells are pre-sensitized and can be loaded with an agent at a later time.

In response to applicant's argument, it is noted that the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Mitchell et al teach that loading two proteins into RBCs by electroporation and the content release of red cells are positively linked to increased pulse length,

Art Unit: 1632

frequency, and intensity of the electric field, they teach using a electric field ranges from 6-8 kv/cm from 5-40 microseconds. *Mitchell et al* load the two proteins at once, and do not use multiple doses of electroporation.

Ortiz et al teach a method of loading CHO cells with two (protein) enzymes using different combinations of single- and double-dose electroporation, they teach that separate loading of two enzymes as an alternative protocol for certain need, and teach that once the cells have been electroporated, they would resist a second electroporation and remain viable (2nd paragraph, right column, page 167).

Here, the first step of loading taught by *Ortiz et al* is considered pre-sensitizing relative to the second step of loading regardless whether *Ortiz et al* expressly suggested the pre-sensitizing, and vice versa, the second step of eletroporation could be considered as a sensitizing step after loading because the method steps are the same. The claims do not require that the pre-sensitizing or sensitizing step excluding the process of loading, particularly considering the sensitizing could be done after loading. Moreover, *Ortiz et al* clearly teach the influence of multiple-electroporation on cell membrane and viability.

Accordingly, it would have been obvious to one of ordinary skill in the art, at the time the invention was made, to modify the methods taught by *Mitchell et al*, and *Ortiz et al* by simply using the protocol of multiple doses of electroporation for loading multiple agents into RBCs with a reasonable expectation of success. The skilled in the art would have been motivated to do so for separate loading of agents or for easier release of

Art Unit: 1632

loaded agent at a later time. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 1, 3, 4, 13-17, 19, 26, 30, and 31 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Mitchell et al* (Biotech Applied Biochem 1990;12:264-75) and *Ortiz et al* (Mutation Res 1995;327:161-9) as applied to claims 1, 3, 13-17, 26, 30, 31 above, and further in view of *Halaka* (US 6,071,480); and the rejection has been modified to include claims 2, 18, and new claims 36-49.

In paper #14, applicants particularly defined the meaning of “diagnostic and therapeutic ultrasound” in page 12. In light of such, it is determined that claim 18 should have been included in this rejection. New claims 38-47 further define and within the scope of claims 4 and 18.

Halaka teaches disrupting particulate with various sonic waves using different power levels to generate different ultrasonic wave frequency.

In paper #14, applicants argue that the teaching of *Halaka* does not address the deficiencies of *Mitchell et al*, and *Ortiz et al*.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Art Unit: 1632

Accordingly, it would have been obvious to one of ordinary skill in the art, at the time the invention was made, to modify the methods taught by *Mitchell et al*, *Ortiz et al*, and *Halaka* by simply choosing various power levels for content release of loaded RBCs with a reasonable expectation of success because it is within the knowledge of the skill in the art to optimize the energy power according to the cells and loading agents. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary. Therefore, the rejection stands.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3, 10, 13-17, 26, 30, and 31 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 19-21 of U.S. Application No. 09/779,186, now U.S. patent 6,495,351. The rejection now applies to new claims 36, 37, 48, and 49. Although the conflicting claims are not

Art Unit: 1632

identical, they are not patentably distinct from each other because the claimed method in the cited patent encompasses the instant claims.

In paper No. 14, applicants indicated that they would consider the filing of a TD upon an indication of allowable subject matter. However, applicants are reminded that the rejection would remain until after the submission of a TD.

Claims 4, 18, 19 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 8-14 of co-pending Application No. 09/748,063. The rejection now applies to new claims 36, 37, 48, and 49.

Applicants fail to respond to the rejection, thus, the rejection stands for reasons of record.

The prior provisional rejection of claims 1, 3, 9, 10, 12, 13, 14, 15, 16, 17, 26, 30, and 31 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 26, 29-37 of co-pending Application No. 09/779,188, is withdrawn because the cited application is now abandoned.

Double patenting over claims 36 and 37, warning.

Claim Objections

Art Unit: 1632

Claims 11 and 12 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

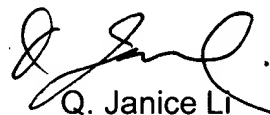
No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).


Q. Janice Li
Examiner
Art Unit 1632

QJL
June 2, 2003